

## **REMARKS**

Claims 20, 32, 36-37 and 108-132 will be pending after entry of the above amendments. Claims 23-28 and 38-107 are canceled. Claims 108-132 are new.

Claim 20 has been amended to recite a range of molar ratios of CaO to D-fructose. Support for this amendment is found, for example, at page 38, lines 13-19. Claim 20 has also been amended to delete steps (b), (c), and (d).

Claim 36 has been amended to delete reference to steps (b) to (f), and to recite additional steps in the process of Example 1 at pages 54-55 of the specification. Claim 36 has also been amended to depend from claim 20.

New claim 108 recites the process of claim 20, further comprising step (b) of claims 20 as originally filed.

New claim 109 recites the process of previously pending claim 23.

New claims 110 and 111 recite the process of previously pending claim 50, and step (b) of claims 20 as originally filed. is also supported, for example, at page 42, lines 16-18 of the specification.. have been amended to recite “sodium bis(2-methoxyethoxy)aluminum hydride/ethanol.” Support for these amendments is found, for example, at page 42, lines 16-18 of the specification.

New claim 112 recites the process of original claim 20, step (d).

New claim 113 recites the process of original claim 25.

New claims 114 and 115 recite the process of original claim 26.

New claims 116 and 117 recite the process of original claim 28.

New claim 118 recites the process of original claim 31.

New claim 119 recites the process of original claim 35.

New claim 120 recites the process of previously pending claim 91.

New claim 121 recites the process of original claim 33.

New claim 122 recites the process of original claim 34.

New claim 123 recites the process of previously pending claim 93, wherein “cytosine” has been replaced with “nucleoside base.” Support for this amendment is found, for example, at page 36, lines 14-26 and page 37, lines 7-8 of the specification.

New claims 124 and 125 recite the processes of previously pending claims 94 and 95. Support for these claims is also found in the specification at page 37, lines 4-32.

New claims 126-130 recite the processes of previously pending claims 96-100, respectively. New claim 130 is also supported by Example 6 at page 58, lines 29-30 of the specification.

New claim 131 is supported by for example, by page 38, line 16 of the specification.

New claim 132 is supported, for example, by Example 1 at page 54 of the specification.

New claim 133 is supported, for example, by page 38, line 17 of the specification, wherein a molar ratio of 2.3 to 1.3 is described.<sup>1</sup>

New claim 134 is supported, for example, by page 54, line 25.

No new matter is added by the amendments. Applicants respectfully request reconsideration of the pending rejections based on the following remarks.

### **Claim Objections**

The Examiner has objected to claims 35 and 102 for allegedly failing to further limit the subject matter of the previous claim. (Office Action, page 2). Claims 35 and 102 have been canceled. Therefore, the claim objections are moot and Applicants respectfully request that the objections be withdrawn.

### **Claims Rejections under 35 U.S.C. § 112**

The Examiner has rejected claims 36 and 92 under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. (Office Action, page 3). Specifically, the Examiner finds the reference in claims 36 and 92 to adding CaO(s) in step (a) of claim 20 to be unclear. (*Id.*). Claims 36 and 92 have been amended to delete reference to the CaO(s) addition step of claim 20. Therefore, Applicants respectfully request that the rejections be withdrawn.

### **Claims Rejections under 35 U.S.C. § 103**

The Examiner has maintained the rejection of the instant claims under 35 U.S.C. § 103(a) as allegedly obvious over BeMiller, *et al.* (“BeMiller”) in view of the Merck Index (“Merck”), Sundberg, *et al.* (“Sundberg”), McFarlin, *et al.* (“McFarlin”) and Piccirilli, *et al.* (“Piccirilli”). The Examiner alleges that the instant claims are obvious because BeMiller teaches the conversion of D-fructose to 2-C-methyl-D-ribonolactone with aqueous calcium

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<sup>1</sup> A molar ratio of 2.3 to 1.3 is equivalent to a molar ratio of 1.8 to 1.

hydroxide, Merck teaches that CaO in water forms aqueous calcium hydroxide, Sundberg teaches that an alkoxyaluminum hydride reagent can be used to reduce a lactone carbonyl group to an alcohol, McFarlin teaches that  $\text{LiAl}(\text{O}^t\text{Bu})_3\text{H}$  is a mild reducing agent, and Piccirilli teaches that certain ribose sugars are synthetic targets for potential therapeutics. (Office Action, pages 4-7). The Examiner has also cited a sixth reference, Ault, Techniques and Experiments in Organic Chemistry, 5<sup>th</sup> Ed., 274-75 (1996) (“Ault”), to add that extraction is a common technique use to separate organic substances. (Office Action, page 6). Applicants respectfully disagree with the Examiner’s conclusion that the instant claims are obvious over these references.

**A. Claims 20, 32, 36-37 and 108-132 are not obvious over the process of BeMiller in view of Merck.**

To make a *prima facie* case of obviousness, the Examiner must “*identify a reason* that would have prompted a person of ordinary skill...to combine the elements in the way the claimed new invention does.” *KSR International Co. v. Teleflex Inc.* 82 U.S.P.Q.2d 1385, 1395 (2007) (emphasis added). Indeed, the mere “identification in the prior art of each component of [an invention] does not show that the combination as a whole...is obvious.” *Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals, Inc.*, 471 F.3d 1369, 1379 (Fed. Cir. 2006). Rather, “the law requires a motivation to select the references and to combine them in the particular claimed manner to reach the claimed invention.” *Id.* (Emphasis added).

Instant claim 20 is not obvious in view of the references cited by the Examiner because the Examiner has failed to demonstrate that one of ordinary skill in the art would have sufficient motivation to modify the process of BeMiller to arrive at the process claimed herein. Claim 20, from which the remaining claims depend, recites, *inter alia*, a process for preparing a 2-C-methyl-D-ribofuranose compound from D-fructose using CaO(s) at a particular molar ratio of CaO to D-fructose. The Examiner alleges that one of ordinary skill in the art would be motivated by BeMiller in view of Merck to replace aqueous calcium hydroxide with CaO in the process of BeMiller. (Office Action, pages 5-6). As Applicants stated in response to the final Office Action dated August 21, 2007, one of ordinary skill in the art would not have been motivated to modify the process of BeMiller to arrive at the process of claim 20 because the BeMiller process already worked for its intended purpose– the conversion of fructose to 2-C-methyl-D-ribonolactone– without the use of CaO. The Examiner has merely pointed to individual components of the instant process without reason as to why one of ordinary skill in the art would modify the process of BeMiller based on the teachings of Merck. Without such

further guidance, one of ordinary skill in the art would have no motivation to replace aqueous calcium hydroxide with CaO. *Eli Lilly & Co.*, 471 F.3d at 1379.

The Examiner attempts to cure this deficiency by alleging that the use of CaO is “preferable in view of [the] Merck Index since it is more soluble in water and dissolves to produce the calcium hydroxide needed for the said conversion.” (Office Action, pages 5-6). The mere fact that Merck teaches that CaO is more soluble in water than calcium hydroxide does not create a motivation to modify the process of BeMiller to use CaO in a specific step as recited in the instant claims, not to mention at the specifically claimed proportions. BeMiller does not teach that the solubility of calcium hydroxide is an important part of the process taught therein. Indeed, BeMiller does not mention that the calcium hydroxide need be dissolved in the solution of D-fructose at all. In sum, the Examiner has not provided a specific reason why one skilled in the art would be motivated to modify the process of BeMiller to add the step of adding CaO(s) at the claimed proportions, to generate calcium hydroxide *in situ*. Without such a motivation, the Examiner has not made a *prima facie* case of obviousness. *See KSR*, 82 U.S.P.Q.2d at 1395; *Eli Lilly & Co.*, 471 F.3d at 1379.

**B. Claims 20, 32, 36-37 and 108-132 are not obvious over the process of BeMiller in view of Merck, Ault, Sundberg, McFarlin and Piccirilli.**

The Examiner has rejected the instant claims as obvious over BeMiller in view of Merck, as discussed above, further in view of Ault, Sundberg, McFarlin and Piccirilli. None of the references cited by the Examiner cure the defects of BeMiller and Merck, because neither Ault, Sundberg, McFarlin nor Piccirilli teach the use of calcium oxide in the preparation of 2-C-methyl-D-ribonolactone. For the reasons discussed above, claim 20 is not obvious over the references cited by the Examiner.

The Examiner further cites Piccirilli to allege that the reaction of a 2-C-methyl-D-ribofuranose with an optionally protected activated nucleoside base is obvious. (Office Action, page 8). Piccirilli does not teach the preparation of 2-C-methyl-D-ribofuranose from D-fructose as recited in the instant claims. Indeed, Piccirilli references an earlier publication for the preparation of 2-C-methyl-D-ribofuranose, wherein an entirely different method of preparation is used. (Piccirilli, page 747, fn. 1). Therefore, Piccirilli adds nothing regarding the use of CaO(s) in the processes of the instant claims. For these reasons, the instant claims are not obvious over the references cited by the Examiner.

**C. The claims are not obvious because Applicants have shown unexpected and superior results over the references cited by the Examiner.**

Even assuming, *arguendo*, that the Examiner has made a *prima facie* case of obviousness, evidence of unexpected or superior results may be used to rebut that conclusion. *In re May*, 574 F.2d 1082, 1094 (C.C.P.A. 1978); *see also In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987); *Ortho-McNeil Pharmaceutical v. Mylan Laboratories*, 348 F. Supp. 2d 713, 755 (N.D. W. Va. 2004). Through experimentation Applicants surprisingly discovered that, compared to the processes of the prior art, the process of the instant claims provided the desired product in a significantly shorter time of reaction. Applicants further found that the product of the claimed process was surprisingly easier to purify over that of the prior art, and that product was thereby obtained in a higher product yield. For these reasons, as discussed further below, Applicants have rebutted any *prima facie* case of obviousness the Examiner may have made.

1. Shortened time of reaction

Applicants surprisingly discovered that the use of CaO in the process of the instant claims allowed for much shorter reaction times compared to the process of BeMiller, the prior art process cited by the Examiner. (*See* page 28, lines 26-30 of the specification). BeMiller teaches that the preparation of the lactone product of step (a) from D-fructose takes approximately 8 to 10 weeks. This extended process is not practicable for large-scale synthetic efforts. In stark contrast, the process of the instant claims allows for the preparation of the lactone of step (a) in 20.5 to 26.5 hours in the above-mentioned higher yield over the process of BeMiller. Submitted herewith is the Declaration of Adel M. Moussa, wherein the results of experiments performed using various molar ratios of CaO to D-fructose are described. (Declaration of Moussa, ¶ 9; *see also* Example 1, page 54 of the specification). The process of the instant claims is much faster than that of BeMiller, even considering the time required for purification steps, optional protection and deprotection steps, and the further reactions of the instant claims to obtain 2-C-methyl-D-ribofuranose and 2'-C-methyl-D-ribonucleoside products. Claims 37, 119-122 and 134 reflect these improved reaction times over that of BeMiller. Therefore, the claimed process is also superior to the prior art processes because of the significantly reduced reaction time required to obtain the product in a higher yield.

2. Ease of purification

Applicants also surprisingly discovered that the process of claim 20 provides a crude product that is easier to purify, compared to the process of BeMiller, which requires the use of an ion exchange column not practicable for large scale syntheses. (Declaration of Moussa, ¶ 13). Claim 36 has been amended to recite the simplified process for purifying 2-C-methyl-D-ribonolactone.

3. Improved product yields

Further, Applicants surprisingly discovered that a molar ratio of CaO to D-fructose of about 5 to 1, to about 1.8 to 1 (2.3 to 1.3) provided higher product yields than the calcium hydroxide process of the prior art. Outside these ranges, Applicants discovered that the product yield was lower. (Declaration of Moussa, ¶ 9). Molar ratios of about 4 to 1, 2 to 1, to about 1.5 to 1 of CaO to D-fructose gave product yields of 13 to 13.6%. (*Id.*). These yields demonstrate that the process of claim 20 is superior to that of BeMiller, which gave only an approximate 10% yield. (*Id.*). Indeed, the process of claim 20 represents a 30 to 36% improvement in yield over the process of the prior art. (*Id.*, ¶ 11). This improvement in yield is especially important for production-scale syntheses of 2-C-methyl-D-ribofuranose. (*Id.*, ¶ 14). For at least this reason, the process of claim 20 is a superior and unexpectedly better method of preparing 2-C-methyl-D-ribofuranose over that of the art cited by the Examiner.

In view of the above unexpected results, which provide an improved method for the large-scale production of 2-C-methyl-D-ribonolactone through improved product yields, shorter reaction times and ease of purification, the instant claims are not obvious. *See In re May*, 574 F.2d at 1094. Therefore, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) be withdrawn.

**D. The Rejection of claims 101-107 is moot.**

The Examiner's rejection of claims 101-107 has been rendered moot by the cancellation of these claims. Applicants reserve the right to later amend the claims to reintroduce the subject matter of claims 101-107, or file one or more continuation of divisional applications reciting the same.

**CONCLUSION**

In view of the foregoing, it is submitted that this application is in condition for allowance. Favorable consideration and prompt allowance of the application are respectfully requested. If the Examiner believes it would be useful to advance prosecution, the Examiner is invited to telephone the undersigned at (858) 314-1200.

A fee for an extension of time of three months will be paid by EFS Web. Please apply any additional fees and any other charges, or any credits, to Jones Day Deposit Account No. 503013 (ref. no. 417451-999027).

Respectfully submitted,

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